

TREATMENT OF CRYPTOCOCCAL MENINGITIS ASSOCIATED WITH THE ACQUIRED IMMUNODEFICIENCY SYNDROME

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ABSTRACT

Background Treatment with low-dose amphotericin B (0.4 mg per kilogram of body weight per day) or oral azole therapy in patients with the acquired immunodeficiency syndrome (AIDS) and cryptococcal meningitis has been associated with high mortality and low rates of cerebrospinal fluid sterilization.

Methods In a double-blind multicenter trial we randomly assigned patients with a first episode of AIDS-associated cryptococcal meningitis to treatment with higher-dose amphotericin B (0.7 mg per kilogram per day) with or without flucytosine (100 mg per kilogram per day) for two weeks (step one), followed by eight weeks of treatment with itraconazole (400 mg per day) or fluconazole (400 mg per day) (step two). Treatment was considered successful if cerebrospinal fluid cultures were negative at 2 and 10 weeks or if the patient was clinically stable at 2 weeks and asymptomatic at 10 weeks.

Results At two weeks, the cerebrospinal fluid cultures were negative in 60 percent of the 202 patients receiving amphotericin B plus flucytosine and in 51 percent of the 179 receiving amphotericin B alone ($P=0.06$). Elevated intracranial pressure was associated with death in 13 of 14 patients during step one. The clinical outcome did not differ significantly between the two groups. Seventy-two percent of the 151 fluconazole recipients and 60 percent of the 155 itraconazole recipients had negative cultures at 10 weeks (95 percent confidence interval for the difference in percentages, -100 to 21). The proportion of patients who had clinical responses was similar with fluconazole (68 percent) and itraconazole (70 percent). Overall mortality was 5.5 percent in the first two weeks and 3.9 percent in the next eight weeks, with no significant difference between the groups. In a multivariate analysis, the addition of flucytosine during the initial two weeks and treatment with fluconazole for the next eight weeks were independently associated with cerebrospinal fluid sterilization.

Conclusions For the initial treatment of AIDS-associated cryptococcal meningitis, the use of higher-dose amphotericin B plus flucytosine is associated with an increased rate of cerebrospinal fluid sterilization and decreased mortality at two weeks, as compared with regimens used in previous studies. Although consolidation therapy with fluconazole is associated with a higher rate of cerebrospinal fluid sterilization, itraconazole may be a suitable alternative for patients unable to take fluconazole. (*N Engl J Med* 1997;337:15-21.)

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C RYPTOCOCCOSIS is the most common life-threatening fungal infection in patients infected with the human immunodeficiency virus (HIV).¹ Before the epidemic of the acquired immunodeficiency syndrome (AIDS), the standard therapy for cryptococcal meningitis was amphotericin B (0.3 mg per kilogram of body weight per day) and flucytosine (150 mg per kilogram per day) for four to six weeks.^{2,3} However, the use of flucytosine in patients with AIDS has been controversial. In one large retrospective study, the addition of flucytosine to amphotericin B was associated with significant toxicity and offered no benefit over amphotericin B alone.⁴

The oral triazole antifungal drugs, fluconazole and itraconazole, are alternatives to amphotericin B, but there are conflicting data on the efficacy of these drugs. The largest prospective study of AIDS-associated cryptococcal meningitis found no difference in outcome between treatment with amphotericin B (0.4 mg per kilogram per day) and treatment with fluconazole, with negative cerebrospinal fluid cultures in less than 50 percent of the patients.⁵ Overall mortality was 14 percent in the amphotericin B group and 18 percent in the fluconazole group; mortality at two weeks was 8 percent and 15 percent, respectively. The results of smaller studies suggest that amphotericin B given in a higher dose (0.7 or 0.8 mg per kilogram per day), either alone or in combination with flucytosine (100 mg per kilogram per day), may be superior to an oral triazole.^{6,7} Thus,

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questions persist about the optimal initial therapy for AIDS-associated cryptococcal meningitis.

The Mycoses Study Group and the AIDS Clinical Trials Group (ACTG) of the National Institute of Allergy and Infectious Diseases designed a multicenter, randomized, double-blind trial to determine the effectiveness of 14 days of higher-dose amphotericin B, with or without flucytosine, as induction therapy in patients with cryptococcal meningitis and to compare fluconazole and itraconazole as consolidation therapy for an additional 8 weeks in patients whose clinical condition had not deteriorated during the induction phase.

METHODS

Study Design

The study was conducted in two steps. In step one, patients with a first episode of AIDS-associated cryptococcal meningitis were randomly assigned to receive amphotericin B (0.7 mg per kilogram per day) with either flucytosine (100 mg per kilogram per day in four divided doses) or placebo for the initial two weeks of therapy. In step two, patients whose condition was stable or improved at the completion of step one were randomly assigned, in a double-blind, placebo-controlled fashion, to consolidation therapy with either fluconazole (a loading dose of 800 mg per day for two days, followed by 400 mg per day for eight weeks) or itraconazole (a loading dose of 600 mg per day for three days, followed by 200 mg twice each day for eight weeks). The study protocol was reviewed and approved by the institutional review board at each study site. All patients provided written informed consent.

Study Population

The criteria for enrollment in step one of the study included HIV infection documented by a positive test for HIV antibody or a previous AIDS-defining opportunistic infection, an age of 13 years or older, and a first episode of cryptococcal meningitis documented by a cerebrospinal fluid culture that was positive for *Cryptococcus neoformans*. Patients were excluded if they had already received a total dose of more than 1 mg of amphotericin B per kilogram or more than 1200 mg of fluconazole, itraconazole, or ketoconazole as treatment for this episode of meningitis. Patients were also excluded if they were comatose; were taking medications that affect the metabolism of itraconazole (e.g., phenytoin, carbamazepine, phenobarbital, or rifamycins) or decrease the absorption of itraconazole (histamine H₂ blockers); were receiving 50 mg or more of hydrocortisone daily; were pregnant or lactating; were unable to take medications by mouth or nasogastric tube; had a history of active hepatitis or moderate-to-severe hematologic, renal, or hepatic dysfunction; or had another acute opportunistic infection requiring therapy during the first two weeks. At the time of the base-line randomization, the patients were stratified according to their mental status (normal, defined as awake and alert, or abnormal, defined as somnolent or obtunded) and the institution at which they were receiving treatment.

The eligibility criteria for step two were a stable or improved clinical condition during the previous 14 days, receipt of a minimal total dose of 7.5 mg of amphotericin B per kilogram, the ability to take oral medications, and hepatic enzyme values that remained lower than 10 times the upper limit of normal and serum bilirubin values that remained lower than 2 times the upper limit of normal. The patients were stratified according to their base-line mental status and the therapy received during step one.

Evaluation

Clinical and laboratory evaluations were performed at base line, twice weekly for the first 2 weeks, weekly for the next 2 weeks,

and then every 2 weeks until the 10-week study period was completed. Studies of cerebrospinal fluid and tests of serum cryptococcal antigen were performed at base line and weeks 2, 4, and 10. The Mini-Mental State Examination was performed at base line and weeks 2 and 10.⁸

Outcomes

Mycologic and clinical outcomes were evaluated separately and together as a composite outcome. At two weeks, the mycologic outcome was considered to be successful if the cerebrospinal fluid fungal culture was negative, and the clinical outcome was considered to be successful if fever, headache, and meningismus were improved or no worse. Successful treatment at 10 weeks was defined mycologically as a negative cerebrospinal fluid fungal culture and clinically as the absence of fever, headache, and meningismus. Toxicity was defined according to the ACTG scale for reporting adverse events.

Statistical Analysis

For both steps, there were two primary evaluations of the outcome: mycologic and clinical. For step one, we assumed that amphotericin B alone would result in cerebrospinal fluid sterilization or clinical stabilization in 20 percent of the patients.⁵ With a two-sided test, an alpha level of 0.05, and a power of 80 percent to detect a true difference of 20 percent in the mycologic outcome at two weeks in the two groups, the analysis would require 182 patients per group.

For step two, our null hypothesis was that the success rate for fluconazole was at least 15 percent higher than that for itraconazole in terms of both clinical and mycologic outcomes. We wanted to determine whether an analysis of our data would reject this hypothesis in favor of the alternative, that the two triazoles were equally effective. If the true success rate for each triazole were 34 percent, an analysis using a one-sided test with an alpha level of 0.025 and a power of 80 percent to detect a difference would require 157 patients per group, for a total of 314 patients.⁹ On the basis of an earlier study, we estimated that 20 percent of patients would not be available for random assignment in step two⁵; consequently, we planned to enroll 400 patients in step one.

The outcome analysis was performed on an intention-to-treat basis. In the case of patients who were not available for a lumbar puncture or evaluation of clinical status at week 2 or 10, treatment was considered to have failed. In the case of patients who died, elevated intracranial pressure was considered to be associated with death if the last known cerebrospinal fluid opening pressure was 250 mm or higher within two weeks before death or if there was no pressure measurement available and the patient had cranial-nerve or other central nervous system findings consistent with elevated pressure or herniation.

The treatment groups were compared by the Kruskal-Wallis test for ordinal measurements and the chi-square test for categorical measurements.¹⁰ The Kaplan-Meier method was used in survival analyses, and the treatment groups were compared by the log-rank test.¹¹ The logistic-regression model was used for multivariate assessment of the relative risk of mycologic failure during therapy, after adjustment for potentially confounding factors.¹² Base-line data associated with successful outcomes at 2 and 10 weeks ($P < 0.30$) in univariate analyses were included in the multivariate models. Cerebrospinal fluid opening pressure was not included in the multivariate model because of the large number of missing data.

RESULTS

Study Population

From October 1991 through August 1994, 408 patients were enrolled in step one of the study. Twenty-seven of these patients were ineligible at base line (19 had negative cerebrospinal fluid cul-

tures, 4 were receiving corticosteroids or rifampin, 2 had had a previous episode of cryptococcal disease, 1 was HIV-negative, and 1 was pregnant). Of the 381 eligible patients, 202 received amphotericin B plus flucytosine and 179 received amphotericin B alone. Demographic characteristics and base-line laboratory values, CD4 lymphocyte counts, and clinical signs and symptoms of cryptococcal disease did not differ significantly between the two groups (Table 1). Eighty-nine percent of the patients were judged to be awake and alert; however, there were behavioral changes in 21 percent.

A total of 306 patients were eligible for randomization in the second step of the study: 151 received fluconazole and 155 received itraconazole. There were no differences between these two treatment groups at the time of the base-line assessments in step two (Table 2). Seventy-five patients were not randomly assigned to a treatment group in step two: 19 died while receiving therapy in step one; 11 had a deterioration in clinical status; 11 had toxic effects necessitating discontinuation of the study drug; 7 were receiving antiepileptic agents, rifampin, or H₂ blockers; 4 had concurrent acute opportunistic infections; 1 did not receive an adequate total dose of amphotericin B; 1 was not alert enough to take oral medications; and 21 withdrew from the study or were lost to follow-up.

Outcomes

Step One

As shown in Table 3, at two weeks, cerebrospinal fluid cultures were negative in 60 percent of the patients who received amphotericin B with flucytosine and in 51 percent of those who received amphotericin B alone (P=0.06). There were no significant differences in the proportions of patients with stable or improved symptoms (78 percent of the combination-therapy group and 83 percent of the amphotericin B group, P=0.18), unchanged or improved scores on the Mini-Mental State Examination (77 percent of the combination-therapy group and 74 percent of the amphotericin B group, P=0.42), or combined mycologic and clinical responses (50 percent of the combination-therapy group and 42 percent of the amphotericin B group, P=0.12). Over the two-week period, the median titer of cerebrospinal fluid cryptococcal antigen declined from 1:1024 at base line in both treatment groups to 1:200 in the combination-therapy group and 1:256 in the amphotericin B group (P=0.56).

Step Two

At 10 weeks, 72 percent of the patients receiving fluconazole had negative cerebrospinal fluid cultures; lumbar punctures were not performed in 39 patients (Table 4). In the itraconazole group, cere-

brospinal fluid cultures were negative in 60 percent of the patients; 54 patients did not have lumbar punctures (95 percent confidence interval for the difference between the percentages of patients with negative cultures in the two groups, -100 to 21). Therefore, we were unable to reject the null hypothesis that fluconazole was 15 percent more effective than itraconazole in terms of the sterilization of cerebrospinal fluid cultures.

With regard to clinical efficacy, 68 percent of the fluconazole recipients and 70 percent of the itraconazole recipients had complete resolution of symp-

TABLE 1. BASE-LINE CLINICAL AND LABORATORY CHARACTERISTICS OF 381 PATIENTS WITH AIDS-ASSOCIATED CRYPTOCOCCAL MENINGITIS TREATED WITH AMPHOTERICIN B PLUS FLUCYTOSINE OR AMPHOTERICIN B ALONE (STEP ONE).*

CHARACTERISTIC	AMPHOTERICIN B + FLUCYTOSINE (N=202)	AMPHOTERICIN B (N=179)
Race or ethnic group (% of patients)		
Non-Hispanic white	32	37
Black	53	45
Hispanic	13	17
Other	2	1
Age (yr)		
Median	37	37
Range	24-65	22-70
Male sex (% of patients)	87	91
Cryptococcosis as first AIDS-defining illness (% of patients)	39	34
CD4 count (per mm ³)		
Median	20	18
Range	0-338	0-220
Previous antiretroviral therapy (% of patients)	27	26
Positive blood culture for <i>C. neoformans</i> (% of patients)†	58	61
Positive CSF India-ink preparation (% of patients)‡	83	82
Serum cryptococcal antigen titer§		
Median	1:4096	1:4096
Range	1:0-1:1,048,576	1:0-1:2,097,152
CSF cryptococcal antigen titer¶		
Median	1:1024	1:1024
Range	1:0-1:16,777,216	1:0-1:524,288
Normal mental status (% of patients)	88	90
Signs or symptoms (% of patients)		
Headache	89	90
Fever	73	77
Meningismus	46	42
Visual changes	29	29
Behavioral changes	22	20
Cough	35	31
Dyspnea	15	11

*None of the differences between the two groups were statistically significant. CSF denotes cerebrospinal fluid.

†Data were available for 168 patients in the combination-therapy group and 138 in the amphotericin B group.

‡Data were available for 175 patients in the combination-therapy group and 157 in the amphotericin B group.

§Data were available for 139 patients in the combination-therapy group and 121 in the amphotericin B group.

¶Data were available for 155 patients in the combination-therapy group and 140 in the amphotericin B group.

TABLE 2. CLINICAL AND LABORATORY CHARACTERISTICS OF THE 306 PATIENTS RANDOMLY ASSIGNED TO CONSOLIDATION THERAPY WITH FLUCONAZOLE OR ITRACONAZOLE (STEP TWO).*

CHARACTERISTIC	FLUCONAZOLE (N = 151)	ITRACONAZOLE (N = 155)
Positive CSF culture for <i>C. neoformans</i> (% of patients)†	23	32
Positive blood culture for <i>C. neoformans</i> (% of patients)‡	4	6
Positive CSF India-ink preparation (% of patients)§	58	52
Serum cryptococcal antigen titer¶		
Median	1:2048	1:1024
Range	1:0–1:1,048,576	1:2–1:4,194,284
CSF cryptococcal antigen titer		
Median	1:256	1:256
Range	1:0–1:32,768	1:0–1:262,144
Normal mental status (% of patients)	100	98
Signs or symptoms (% of patients)		
Headache	34	39
Fever	24	20
Cough	14	11
Meningismus	6	7

*None of the differences between the two groups were statistically significant. CSF denotes cerebrospinal fluid.

†Data were available for 107 patients in the fluconazole group and 113 in the itraconazole group.

‡Data were available for 71 patients in the fluconazole group and 65 in the itraconazole group.

§Data were available for 120 patients in each group.

¶Data were available for 96 patients in the fluconazole group and 97 in the itraconazole group.

||Data were available for 113 patients in the fluconazole group and 112 in the itraconazole group.

TABLE 3. OUTCOME AT TWO WEEKS (STEP ONE).

OUTCOME	AMPHOTERICIN B + FLUCYTOSINE		P VALUE*
	(N = 202)	AMPHOTERICIN B (N = 179)	
	no. of patients (%)		
Cerebrospinal fluid culture			0.06
Negative	122 (60)	91 (51)	
Positive†	80 (40)	88 (49)	
Fever, headache, and meningismus unchanged or improved	157 (78)	149 (83)	0.18
Combined mycologic and clinical response	102 (50)	76 (42)	0.12
Score on Mini-Mental State Examination			0.42
Unchanged or improved	156 (77)	132 (74)	
Worse‡	46 (23)	47 (26)	

*P values were determined by the chi-square test.

†Included in this category are 33 patients in each group in whom lumbar punctures were not performed.

‡Included in this category are 26 patients in the combination-therapy group and 21 in the amphotericin B group for whom data were not available.

TABLE 4. OUTCOME AT 10 WEEKS (STEP TWO).

OUTCOME	FLUCONAZOLE (N = 151)	ITRACONAZOLE (N = 155)	95% CI*
	no. of patients (%)		
Cerebrospinal fluid culture			–100 to 21
Negative	109 (72)	93 (60)	
Positive†	42 (28)	62 (40)	
Fever, headache, and meningismus absent	102 (68)	108 (70)	–100 to 7
Combined mycologic and clinical response	64 (42)	73 (47)	–100 to 5
Score on Mini-Mental State Examination			–100 to 6
Unchanged or improved	102 (68)	109 (70)	
Worse‡	49 (32)	46 (30)	

*The confidence intervals (CI) are for the difference between the percentages of patients with negative cultures in the two groups.

†Included in this category are 39 patients in the fluconazole group and 54 in the itraconazole group in whom lumbar punctures were not performed.

‡Included in this category are 33 patients in the fluconazole group and 38 in the itraconazole group for whom data were not available.

toms (headache, fever, and meningismus). On the Mini-Mental State Examination, 68 percent of the fluconazole recipients and 70 percent of the itraconazole recipients had unchanged or improved scores. Thus, in terms of clinical success, there was no significant difference between the treatment groups, and the null hypothesis that the clinical efficacy of fluconazole was 15 percent greater than that of itraconazole was rejected.

Over the eight-week period of consolidation therapy, the median titer of cerebrospinal fluid cryptococcal antigen declined in both treatment groups, from 1:256 in both groups at 2 weeks to 1:57 in the fluconazole group and 1:32 in the itraconazole group at 10 weeks (P=0.22). The four treatment combinations did not differ significantly with regard to cerebrospinal fluid culture sterilization, resolution of clinical symptoms, or survival at 10 weeks (data not shown).

Deaths

During step one, 21 patients died (5.5 percent): 11 of the 202 patients in the amphotericin B group and 10 of the 179 in the combination-treatment group (P=0.65 by the log-rank test). During step two, there were 2 deaths among the 151 fluconazole recipients and 5 among the 155 itraconazole recipients; an additional 2 fluconazole recipients and 3 itraconazole recipients died during weeks 3 to 10 but were not receiving the study drug at the time (P=0.27, by the log-rank test, for total deaths). Thus, 12 of the 306 patients (3.9 percent) in step two died. Seven other patients who had been enrolled in step one but were not randomly assigned to treatment in step two died during weeks 3 to 10.

Cerebrospinal Fluid Opening Pressure

During step one, the median base-line cerebrospinal fluid opening pressure was 220 mm in the 123 patients with negative cerebrospinal fluid cultures at two weeks and 280 mm in the 97 with persistently positive cultures ($P=0.01$). Of the 14 patients who died and for whom cerebrospinal fluid opening pressures were determined, 13 had pressures higher than 250 mm at the time of the last lumbar puncture. Six of these patients also had cranial-nerve abnormalities or palsies, ataxia, or herniation. Two patients in whom opening pressures were not measured had ataxia or a clinical diagnosis of elevated intracranial hypertension; both patients died.

Factors Predicting Outcome

We performed a multivariate analysis of base-line characteristics associated with a negative cerebrospinal fluid culture at 2 weeks and at 10 weeks (Table 5). Data were available for 268 patients at 2 weeks and 306 patients at 10 weeks. An elevated base-line serum creatinine value ($P=0.04$), treatment with amphotericin B plus flucytosine ($P=0.01$), the presence of fever ($P=0.02$), and a negative blood culture for *C. neoformans* ($P=0.001$) were independently associated with a negative cerebrospinal fluid culture at two weeks. Factors significantly associated with a negative culture at 10 weeks, after adjustment for the covariate of time, were the absence of intravenous drug use ($P=0.03$), fluconazole therapy ($P=0.02$; odds ratio, 1.78), and a negative cerebrospinal fluid culture at 2 weeks ($P=0.01$). A multivariate logistic-regression analysis showed that the study treatment was not associated with a clinical benefit at 2 or 10 weeks.

Drug Toxicity

Step One

Eleven patients (2.9 percent) had toxic effects requiring the withdrawal of the study drug (six receiving combination therapy and five receiving amphotericin B alone). Three patients had elevated serum creatinine values, two had nausea, two had hypokalemia, and one each had a rash, headache, hemolytic anemia, and a gastrointestinal hemorrhage. Overall, there were no differences in toxic effects between the treatment groups, regardless of whether the base-line hematologic values were normal or abnormal. Among the patients with normal serum creatinine values at base line, 1 percent in each group had values that were more than three times the upper limit of normal during the two weeks of treatment.

Step Two

During step two, 12 patients (6 in each group) had toxic effects requiring the withdrawal of the study drug. Six patients had nausea and vomiting,

TABLE 5. MULTIVARIATE ANALYSIS OF BASE-LINE CHARACTERISTICS ASSOCIATED WITH NEGATIVE CEREBROSPINAL FLUID CULTURES AT 2 AND 10 WEEKS.

CHARACTERISTIC	ODDS RATIO (95% CI)*	P VALUE
Negative culture at 2 weeks†		
Presence of fever	2.03 (1.31–2.44)	0.02
Elevated serum creatinine level	2.38 (1.03–5.52)	0.04
Negative blood culture for <i>C. neoformans</i>	2.41 (1.42–4.10)	0.001
Treatment with amphotericin B and flucytosine	1.92 (1.15–3.22)	0.01
Negative culture at 10 weeks‡		
No intravenous drug use	1.82 (1.07–3.09)	0.03
Negative culture at 2 weeks	1.87 (1.13–3.08)	0.01
Treatment with fluconazole	1.78 (1.09–2.90)	0.02

*CI denotes confidence interval.

†The analysis is based on data from 268 patients. In an analysis of 372 patients that included only fever, night sweats, cerebrospinal fluid protein level, alkaline phosphatase level, and flucytosine use, an elevated cerebrospinal fluid protein level was also significantly related to a successful outcome, in addition to the other factors listed.

‡The analysis is based on data from 306 patients.

two of whom had elevated serum creatinine values. Two patients had rashes, including one patient receiving fluconazole, who had the Stevens–Johnson syndrome and survived. One patient each had hyperkalemia, headache, neutropenia, and hepatic failure. Two of these patients died (the patient with hepatic failure and the patient with hyperkalemia); both were in the itraconazole group. Overall, 28 percent of the patients had hematologic toxic effects, 7 percent had hepatic toxic effects, and 4 percent had renal toxic effects.

DISCUSSION

This study was designed to address a number of critical questions in the management of AIDS-associated cryptococcal meningitis: Does the addition of flucytosine offer any advantage over amphotericin B alone? Are the triazole antifungal drugs, fluconazole and itraconazole, equally effective after initial treatment with amphotericin B? Do higher doses of amphotericin B lead to a reduction in the mortality rates reported in previous studies (14 to 18 percent)?

Both in vivo and in vitro data suggest that flucytosine has at least an additive effect, if not a synergistic effect, when combined with amphotericin B.^{13,14} In the era before AIDS, the combination regimen of flucytosine (150 mg per kilogram per day) and low-dose amphotericin B (0.3 mg per kilogram per day) for 6 weeks was equivalent to or better than amphotericin B alone (0.4 mg per kilogram per day) for 10 weeks, with regard to cures, relapses, and rates of cerebrospinal fluid sterilization.² In contrast, among patients with AIDS and cryptococcal disease

evaluated retrospectively, the combination of flucytosine (75 to 100 mg per kilogram per day) and amphotericin B did not alter survival, as compared with amphotericin B alone; in addition, in 53 percent of the patients receiving combination therapy, flucytosine had to be withdrawn because of drug-associated cytopenias.⁴ A small study showed that treatment with higher doses of amphotericin B (0.7 mg per kilogram per day) combined with flucytosine (150 mg per kilogram per day) was dramatically successful.¹⁵

In our study, the addition of lower-dose flucytosine (100 mg per kilogram per day) to amphotericin B for the first two weeks of therapy was not associated with a statistically significant benefit in the univariate analysis, although the rate of cerebrospinal fluid sterilization was higher with the combination regimen than with amphotericin B alone. The addition of flucytosine was independently associated with a better outcome in the multivariate analysis. Moreover, in our study, the addition of flucytosine to amphotericin B was not associated with an increased incidence of toxic effects, probably because of the shorter duration of flucytosine therapy and the use of a daily dose lower than those in a previous study.⁴

For the consolidation phase (step two), we were unable to reject the null hypothesis that fluconazole was 15 percent more effective than itraconazole in terms of cerebrospinal fluid sterilization. The multivariate analysis showed a significant association between fluconazole therapy and negative cultures at 10 weeks. The clinical efficacy of fluconazole and itraconazole was similar with respect to the resolution of symptoms, scores on the Mini-Mental State Examination, and the mortality rate.

One possible reason for the different culture results in the two groups in step two is the difference in the number of patients who did not have lumbar punctures at 10 weeks (54 of the 155 itraconazole recipients vs. 39 of the 151 fluconazole recipients), since the mycologic outcome in these patients was considered to be unsuccessful. Among the study participants who underwent lumbar punctures at week 10, the cerebrospinal fluid culture was negative in 97 percent of those receiving fluconazole (109 of 112) and in 92 percent of those receiving itraconazole (93 of 101). Just as we found that fluconazole resulted in a higher rate of cerebrospinal fluid sterilization than itraconazole, a separate study comparing a lower dose of fluconazole (200 mg per day) with itraconazole (200 mg per day) has clearly shown that fluconazole is superior as maintenance therapy in suppressing cryptococcal infection.¹⁶

Mortality rates for AIDS-associated acute cryptococcal meningitis have ranged from 14 percent among patients receiving amphotericin B alone in our most recent trial to over 25 percent in some trials of

azoles as initial therapy.^{5,17} Most of the deaths occurred during the first two weeks of therapy. Thus, to our knowledge, the mortality rates in our current study (5.5 percent in the first two weeks and 3.9 percent in the next eight weeks) represent the best outcome reported thus far in a large, randomized trial.

The higher dose of amphotericin B in our study (0.7 mg per kilogram per day), with or without flucytosine, may account, in large part, for the low mortality rate. The increased dose of amphotericin B also resulted in a 50 percent rate of cerebrospinal fluid sterilization at two weeks without significant toxicity, which is substantially better than the 20 percent sterilization rate reported in our previous large study of AIDS-associated cryptococcal meningitis, in which the dose of amphotericin B was 0.4 mg per kilogram per day.⁵ We believe these two studies are comparable, since the patients in the previous study had similar base-line characteristics, including positive blood cultures in 53 percent, abnormal mental status in 27 percent, and a median cerebrospinal fluid white-cell count of 5 cells per cubic millimeter. The patients in the previous study had lower median titers of cryptococcal antigen in serum (1:1000, $P < 0.001$) and in cerebrospinal fluid (1:512, $P < 0.001$) at base line and thus presumably had a lower fungal burden. In a recent study, an even higher dose of amphotericin B (1 mg per kilogram per day), with or without flucytosine, for two weeks, followed by fluconazole or itraconazole, resulted in a successful outcome in 29 of 31 patients (94 percent), with no deaths due to cryptococcal disease.¹⁸

Careful management of elevated intracranial pressure is another important factor that probably played a part in the improved outcome in this study. High pressures have been associated with catastrophic neurologic deterioration and death in the absence of hydrocephalus.¹⁹ Almost all the early deaths in this study (13 of 14) and 40 percent of the deaths during weeks 3 through 10 were associated with elevated intracranial pressure. Our study protocol included a treatment algorithm for the management of increased pressure, including daily lumbar punctures, use of acetazolamide, and ventriculoperitoneal shunts for asymptomatic patients with intracranial cerebrospinal fluid pressures higher than 320 mm and for symptomatic patients with pressures higher than 180 mm. Further research is needed to examine this association and determine whether a reduction of high pressure can, in fact, decrease mortality.

In summary, induction treatment for two weeks with the combination regimen of higher-dose amphotericin B plus flucytosine, followed by consolidation therapy with oral fluconazole, is safe and effective and should now be considered the treatment of choice for AIDS-associated cryptococcal meningitis.

In view of the positive influence of flucytosine therapy on the mycologic outcome (in our multivariate analysis), its low degree of toxicity in our study, and recent data demonstrating its effectiveness in preventing relapses (regardless of the maintenance regimen), we believe that the addition of flucytosine to amphotericin B is warranted for induction therapy.¹⁶ For consolidation therapy, itraconazole is a suitable alternative for patients unable to take fluconazole. The strong association between elevated intracranial pressure and early death in our study should encourage clinicians to monitor cerebrospinal fluid pressure even in the absence of symptoms and initiate aggressive management if the pressure is elevated.

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We are indebted to the numerous referring physicians and to the 408 patients whose participation made this study possible. We dedicate this paper to them.

APPENDIX

The following institutions and investigators contributed to the study: *Mycoses Study Group*: Operations Office, Birmingham, Ala. — L. Riser and C. Thomas; Veterans Affairs Medical Center and Baylor College of Medicine — C. Lacke and A.C. White; University of Alabama at Birmingham — S. Patterson, D. Davis, and C. Flanigan; University of Texas at San Antonio — T. Harden and D. Phillips; Detroit Medical Center — L. Ullom and J. Vasquez; George Washington University Medical Center — S. McMullen; University of Texas, Houston — D. Flowers and M. Bosh; Medical College of Virginia — M. Britton; Medical College of Georgia — J.F. Fisher, C. Newman, and B. Willis; University of Mississippi Medical Center — H. Henderson; St. Michael's Medical Center — E. Johnson and L. Dungo; Vanderbilt University — M. Pierce and M. Morgan; Pennsylvania Hospital — J. Stern and N. Petrosky; University of Missouri, Kansas City — D. Bamberger and R. Farnan; Johns Hopkins University — J. Feinberg, L. Apuzzo, and W. Royal; Emory University — S. Thompson and K. Barrett; University of Michigan — C. Kauffman and H. Gutsch; Infectious Diseases Associates of Kansas City — D. McKinsey and B. Lee; Tulane University — N. Hyslop, D. Greenspan, and R. Strata; Permanente Medical Group — W.J. Fessel and G. Van Raalte; and the Ochsner Clinic — G. Pankey.

AIDS Clinical Trials Group: Data Center, Frontier Sciences and Technology Research Foundation, Amherst, N.Y. — D. Schneider; Operations Office, Social and Scientific Systems, Bethesda, Md. — N.D. Briggs and D. Pierce; University of North Carolina at Chapel Hill — S. Lee, I. Vangness, and B. Longmire; University of California at San Francisco — J. Stansell, M. Jacobson, D. Gray, and R. Coleman; Washington University — J. Voorhees, M. Klebert, and M. Royal; Beth Israel Medical Center — D. Mildvan; Yale University — G. Friedland, E. Cooney, and M. Walesky; University of Southern California — J.M. Leedom, R. Larsen, and D. Diamond; Indiana University — L.J. Wheat, H. Nixon, and J. Craft; Ohio State University — J.L. Neidig, R.J. Fass, and J. Russell; University of Pennsylvania — R.R. MacGregor, R. Kappes, and A. Tselis; University of Cincinnati — K.J. Skahan, B. Jackson, P. Daniel, and C. Paulson-White;

University of Rochester — R. Hewitt, S. Cohn, M. Lewis, and C. Greisberger; Harvard University — H. Heller, A. Sugar, A.W. Karchmer, and H. Fitch; Harlem Hospital Center — R. Flam, M. Joseph, and W. El-Sadr; University of Massachusetts — S.H. Cheeseman, K.K. Lai, and M. Sands; Albert Einstein College of Medicine — R. Sociro, D. Stein, and B. Zingman; University of Texas, Galveston — R. Pollard, S. Hausrath, and K. Werman; Cornell University — K. Squires and L. Ponticello; and St. Luke's-Roosevelt Medical Center — M. Grieco.

National Institute of Allergy and Infectious Diseases: R. Hafner and D. Dixon.

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CORRECTION

Treatment of Cryptococcal Meningitis

To the Editor: The conclusion of van der Horst et al. (July 3 issue)¹ that the combination regimen of higher-dose amphotericin B plus flucytosine, followed by consolidation therapy with oral fluconazole, is safe and effective and should now be considered the treatment of choice for AIDS-associated cryptococcal meningitis cannot be supported by the study design or the 10-week outcomes. This two-stage design has a significant bias — the healthy-survivor effect — in that only healthy survivors were permitted to enroll in the consolidation phase of the trial. The data analysis does not address the censoring effect of eliminating patients with a poor prognosis from the azole-therapy arms. The clinical and mycologic responses observed at 10 weeks depend on successful clinical completion of step one and enrollment in step two. In an intention-to-treat analysis that included all enrolled eligible patients, 178 of 381 (47 percent) had favorable combined clinical and mycologic responses at 10 weeks. This combined response rate may not differ from that at 10 weeks for amphotericin B used alone (40 percent; 95 percent confidence interval, 26 to 53 percent) and may be inferior to rates of success for the combination-therapy regimens of amphotericin B plus flucytosine (100 percent; 95 percent confidence interval, >54 percent) or fluconazole plus flucytosine (63 percent; 95 percent confidence interval, 48 to 82 percent).^{2,3,4} In addition, it appears that there may be a clinically significant difference in outcome at 10 weeks if the cerebrospinal fluid culture obtained at week 2 is negative, not positive. The patients with negative cerebrospinal fluid cultures at week 2 had a >92 percent success rate at 10 weeks, implying a significantly lower response rate for those with positive cultures. Thus, a strategy of changing therapy to an azole at two weeks may be ill advised for those patients not known to have negative cerebrospinal fluid cultures even if they seem clinically improved.

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To the Editor: In the report by van der Horst et al., much weight is given to a higher rate of negative cerebrospinal fluid cultures at two weeks in the flucytosine arm. In order to judge the importance of this finding, it is necessary to determine its clinical significance. Did patients with positive cerebrospinal fluid cultures at week 2 fare any worse during follow-up? Is there a difference in rates of later relapse or mortality among patients with successful clinical outcomes between those with positive and those with negative cultures? Did patients with positive cultures at week 2 also have poor cerebrospinal fluid cryptococcal-antigen responses as compared with base line? A change in the level of antigen in the cerebrospinal fluid has been correlated with response and relapse in previous studies.¹ . . .

Of the 14 patients who died and had cerebrospinal fluid opening pressures recorded, 13 had elevated pressures at their last lumbar puncture. We might expect that patients dying of cryptococcal meningitis would have increased cerebrospinal fluid pressures as their conditions deteriorated. How many patients were known to have high opening pressures at base line? Was a high base-line opening pressure predictive of mortality or clinical failure in the group as a whole?

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The authors reply:

To the Editor: Dr. Larsen expresses concern about our study design and a potential bias effect on the outcome. There is no important bias from a "healthy-survivor effect" in our study. Of the 381 patients who participated in step one, 42 (11 percent) reached the study end point or were not eligible for step two. Among the other 33 patients not continuing on to step two, 21 withdrew voluntarily and 12 were excluded because of concomitant medications. Even if all 33 of these patients were deemed "unhealthy" survivors, 80 percent of our step-one patients advanced to step two, and 30 percent had positive cultures at the end of week 2.

Dr. Larsen's extrapolation of our 2-week results to reflect 10-week results and his comparison with previous studies are inappropriate. Of the 306 patients randomly assigned to consolidation therapy, 57 percent were nonresponders (composite response) at 2 weeks, but 65

percent of these showed a composite response at 10 weeks. Thus, Dr. Larsen's assumption that no patients responded to consolidation with azole therapy is incorrect. In addition, the intention-to-treat design of our study required a negative cerebrospinal fluid culture at week 10 for success; if a cerebrospinal fluid culture was not obtained from a patient the treatment was judged a mycologic failure in that patient. Of the 306 step-two patients, 83 did not have week-10 cultures, and the treatment was therefore classified as a failure in those patients. The overall composite response at week 10 was at least 45 percent, and the overall clinical response rate was 69 percent. Moreover, our two-week survival rate of 5.5 percent was strikingly low. Dr. Larsen also alludes to a study with a success rate of 100 percent among patients receiving amphotericin B plus flucytosine.¹ These results were obtained in a small cohort of six patients who had normal mental status at base line (low risk for progression). In another small, nonrandomized trial, the use of flucytosine plus fluconazole did indeed achieve a 63 percent "success" rate; however, serious toxicity occurred in 62 percent of the participants, and 28 percent had to stop therapy because of severe toxicity.² Accordingly, we believe that our conclusion is justified: Higher-dose amphotericin B plus flucytosine followed by consolidation with oral fluconazole should now be considered the treatment of choice for AIDS-associated cryptococcal meningitis.

With respect to Dr. Larsen's final point and to Dr. Zingman's letter, the patients who had positive cultures at week 2 did indeed have a higher risk of positive cultures at week 10. However, there was no difference in long-term outcome with regard to relapse or survival based on a positive culture at week 2. Moreover, in a separate study of maintenance therapy, the relapse rate over a period of 12 months among patients who received flucytosine plus amphotericin B during the first 2 weeks of therapy was significantly lower than the rate in patients who did not receive flucytosine.³ With regard to Dr. Zingman's last point, elevated base-line cerebrospinal fluid opening pressures did predict mortality; however, elevated pressure was not associated with mycologic failure or relapse.

There was an error in our published report, on page 18, in the first sentence under the heading "Deaths." It should have read, "During step one, 21 patients (5.5 percent) died: 11 of 179 in the amphotericin B group and 10 of 202 in the combination group. . . ."

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